IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS

IN RE: TESTOSTERONE REPLACEMENT THERAPY PRODUCTS LIABILITY LITIGATION	MDL No. 2545 Master Docket Case No. 1:14-cv-01748 Honorable Matthew F. Kennelly
This document applies to: *Brad Martin,, et al. v. Actavis, Inc.,, et al.,* Case No. 15-cv-4292 *Casey Brubaker,, et al. v. Actavis, Inc.,, et al.,* Case No. 15-cv-426	

PLAINTIFFS' MEMORANDUM OF LAW IN OPPOSITION TO MOTION OF THE ACTAVIS DEFENDANTS TO EXCLUDE EXPERT TESTIMONY

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INTRODUCTION

Defendants Actavis, Inc., Actavis Pharma, Inc., and Actavis Laboratories UT, Inc. ("Actavis") move to exclude the expert testimony of B. Burt Gerstman, Ph.D., Martin T. Wells, Ph.D., and Hossein Ardehali, M.D. that testosterone therapy can cause cardiovascular events, including myocardial infarction (and, in the case of Dr. Wells, the statistical basis for that conclusion) – opinions that are substantially similar to those this Court has previously held to be admissible from these same witnesses. Actavis also moves to Dr. Ardehali's case-specific opinions that Actavis's product, Androderm, caused the myocardial infarctions suffered by Plaintiffs Martin and Brubaker. Actavis lastly moves to exclude the expert testimony of Robert Johnson regarding the financial condition of Actavis plc, the parent company of the Actavis entities that are parties here. Actavis' motion should be denied in its entirety because Plaintiffs' experts' testimony is admissible under Rule 702. As discussed below, each expert is fully qualified to offer opinions in his field; the methodologies employed in each report have already been found to be reliable; and each opinion is relevant to, and properly fits the facts of, the cases in which it is being offered. As described below, Plaintiffs' experts will help the jury understand how and to what extent Androderm increases the risk of myocardial infarction in the men for whom Actavis intended it to be prescribed and what the various studies of testosterone therapy that have been performed have shown. Plaintiffs' experts provide evidence of general causation – that Androderm was capable of causing Plaintiffs' heart attacks – and specific causation – that Androderm was a substantial contributing factor in causing Plaintiffs' heart attacks. All of this testimony is admissible and should not be excluded.

First, Actavis' attacks on the experts' use of statistical evidence should be rejected. Actavis takes issue with Plaintiffs' experts' reliance upon several studies that identify composite endpoints. However, as Dr. Wells explained, composite endpoints are a recognized tool and are particularly helpful where the component data sets are small. Even Actavis' expert agrees that composite endpoints are appropriate and reliable in the context of small data sets. Plaintiffs' experts correctly utilized composite endpoints, specifically those with cardiovascular events where component endpoints were especially small. To the extent that Actavis disagrees with the experts' use of

composite endpoints, that is a matter for cross-examination, not a basis for exclusion. Actavis also disputes Plaintiffs' experts' utilization of Bayesian meta-analyses because the subject data sets were too small. But, as Dr. Wells testified, small data sets are not as important as plotting and observing the distribution in determining the propriety of the particular type of meta-analysis being implemented. Here, Dr. Wells testified that the meta-analyses distributions confirmed they were properly and reliably implemented.

Second, Actavis argues that Plaintiffs' experts' opinions regarding the mechanisms by which testosterone therapy causes injury are unreliable. For each mechanism, Actavis' argument relies entirely on concerns with one or two studies while ignoring the numerous other studies and publications that Plaintiffs' experts have relied upon in forming their opinions on each mechanism. Plaintiffs' experts appropriately and reasonably rely on the totality of the evidence in supporting their opinions that increases in estradiol, hematocrit, platelet activity, and plaque volume can increase the risk of cardiovascular injuries. Plaintiffs' experts also reasonably rely upon animal and *in vitro* studies to supplement those opinions.

Third, Actavis puts forth arguments about the Vigen and Finkle studies nearly identical to those offered by AbbVie with respect to those studies. This Court has already rejected those arguments and found the Vigen and Finkle studies to be reliable sources for Plaintiffs' experts' consideration. and soundly rejected by the Court during previous bellwether briefing. The Court should do so once again.

Finally, Actavis alleges that Plaintiffs Martin and Brubaker, who were in 52 and 41 years of age, respectively, when they suffered heart attacks, were simply too young for any of Plaintiffs' experts' opinions to apply to them. However, Plaintiffs' experts appropriately relied on a study that observed that cardiovascular risk may triple in men under 65. Moreover, the various mechanisms of injury and the numerous publications and studies considered by Dr. Gerstman and Dr. Ardehali help shed light on different population pools, such as men in their 30s and 40s.

As to case-specific arguments, Dr. Ardehali's methodology of ruling in Androderm as a substantial contributing factor in Plaintiffs' injuries is entirely consistent with the well-supported

opinions delineated in his general causation report, particularly those relating to the various mechanisms through which testosterone can cause cardiovascular events. It is through a combination of his reliance on his general causation report and the presentation of Plaintiffs' specific injuries that Dr. Ardehali is able to ascertain the exact mechanisms at issue in these cases. Doing so allows him to reliably rule in Androderm as a substantial contributing factor with far greater precision and specificity than even that demanded by *Daubert*. More importantly, this is the exact methodology the Court has already admitted. Dr. Ardehali also considered the individual risk factors for each Plaintiff. He reviewed EKG results, cardiac catheterization reports, and scoured relevant testimony in order to reach his own conclusions on what conditions Plaintiffs had at the time of their injuries and the relative cardiovascular risk of each of those conditions in light of their testosterone use. Using all of this information, Dr. Ardehali formed the opinion that Androderm was a substantial contributing factor in causing both Plaintiffs' injuries. Actavis' arguments really are not attacks on Dr. Ardehali's methodology. Instead, they represent mere disagreements with the conclusions that he drew from the pertinent medical evidence – disagreements that can only be resolved by a jury.

Lastly, Robert Johnson's opinion regarding Actavis plc's financial condition will assist the trier of fact and is not overly prejudicial. Moreover, because Actavis plc failed to appear for the properly noticed deposition pursuant to Rule 30(b)(6), Plaintiffs are filing a contemporaneous motion for sanctions against the Actavis Defendants for failing to attend the 30(b)(6) deposition and for failing to produce requested documents. In that motion, Plaintiffs request that, as a discovery sanction, the Court deny Actavis' motion to exclude the expert testimony of Robert Johnson. Plaintiffs incorporate those arguments here as an additional basis on which Actavis' motion to exclude the testimony of Mr. Johnson should be denied.

PLAINTIFFS' EXPERTS

At issue here are the opinions of four of Plaintiffs' experts regarding general causation, specific causation, statistics[1], and economics as follows:

[1] Although Actavis refers to Dr. Martin Wells as a "causation" expert, Dr. Wells is a biostatistician

B. Burt Gerstman, Ph.D.

Dr. Burt Gerstman is an epidemiologist with a Masters of Public Health from the University of California, Berkeley, and a Ph.D. in Epidemiology & Comparative Pathology from the University of California, Davis. He is currently a Professor of Health Science at San Jose State University, in San Jose, California where he teaches epidemiology and biostatistics. His research areas include the history of epidemiology and public health, drug safety, and linked medical record systems. Prior to assuming his position at San Jose State, Dr. Gerstman was an Epidemiology Fellow and then a staff epidemiologist at the Center for Drug Evaluation and Research in the Office of Surveillance and Epidemiology at the U.S. Food and Drug Administration ("FDA"), where his responsibilities included post-marketing surveillance of drug safety, data base development, and training of NIH Epidemiology Fellows and CDC Epidemic Intelligence Officers.

Dr. Gerstman is widely published in the areas of epidemiology and biostatistics. He has published basic textbooks in each of those fields. He has also published numerous articles in peer-reviewed journals, including (among others) articles about the use of mathematical models for health professionals, methods for pharmacoepidemiologic analysis, assessment of drug-associated risk, use of pharmacoepdemiologic databases, as well as oral contraceptives and their link to deep vein thromboembolism. This Court has already found Dr. Gerstman qualified to offer opinions in this MDL in connection with cases involving the AbbVie Defendants. *See* CMO 46. Dr. Gerstman was previously found qualified to offer opinions about the relative safety of different formulations of estradiol-containing oral contraceptives with respect to the increased risk of venous thromboembolism. *See In re Yasmin & YAZ (Drospirenone) Mktg., Sales Practices & Prod. Liab. Litig.*, No. 3:09-MD-02100-DRH, 2011 WL 6302573, at *10 (S.D. Ill. Dec. 16, 2011).

As set forth in his expert report, Dr. Gerstman offers the opinion that

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who does not offer any opinions about causation. Rather, he offers statistical opinions regarding certain studies, and those opinions are relied on, or supportive of the opinions offered by, Plaintiffs' experts who do offer causation opinions.

> There is substantial and credible evidence to indicate that testosterone supplementation increases the risk of heart attack and stroke in older men. Based on the synthesis of data and lines of reasoning in this report, this increase is on the order of 30 to 50% in relative terms, which is roughly equivalent to a risk difference of 4 per 1000, depending on the baseline rate in the population of users.[2]

See Ex. 1 at 11; 138. As detailed in the report, this conclusion is based on a thorough analysis of 18 published observational studies, published studies reporting on several randomized controlled trials ("RCTs"), including the Testosterone in Older Men ("TOM") trial and the T-Trials, and nine published meta-analyses of RCTs of testosterone, covering more than 45 separate published studies. *See generally* Ex. 1. Dr. Gerstman assessed each of the studies he reviewed, evaluating the strengths and weakness of the study design and the reliability of the conclusions drawn by the authors of each of the studies. *Id.* He assessed the various study endpoints and the variations in definitions across the different studies. *Id.* He carefully considered the weight assigned to the numerous underlying studies by the most significant of the meta-analyses. *Id.* Dr. Gerstman specifically considered whether the association between testosterone therapy and heart attacks and strokes reflected in these studies was causal and, using the standard method for epidemiologists considering causation, concluded that it was. *Id.*

In connection with the AbbVie bellwether cases, this Court denied a motion to exclude Dr. Gerstman's general causation opinions. *See* CMO 46. Dr. Gerstman offered a general causation opinion for the Auxilium bellwether cases and the Auxilium Defendants did not seek to exclude it.

Martin Wells, Ph.D

Dr. Martin T. Wells is a chaired Professor of Statistical Sciences at Cornell University, where he is also a Professor of Biological Statistics and Computational Biology. *See* Ex. 2, Wells Report at 1. He serves on the faculty of Weill Medical School at Cornell University, where he is a Professor of Biostatistics in Public Health as well as Clinical Epidemiology and Health Services Research. *Id.* He holds an appointment at Cornell Law School. *Id.* He has a Ph.D in mathematics from the University

[2] Dr. Gerstman's report also discloses opinions concerning the efficacy of testosterone supplementation in men who do not have classical hypogonadism. Those opinions are not at issue on this motion.

of California. *Id.* at 20. He teaches statistical methodology to undergraduate and graduate students, has served on national statistical committees and has published articles in leading statistical and scientific journals. *Id.* at 1, 20-32. He is on the editorial boards of Journal of Multivariate Analysis and Journal of Empirical Legal Studies, and serves as Associate Editor for Annals of Statistics. *Id.* He previously served as an Editor of The Journal of the American Statistical Association, Statistical Science, and Editor-in-Chief of the ASA-SIAM Series on Statistics and Applied Probability. *Id.* He is a Fellow of the American Statistical Association, the Royal Statistical Society, Institute of Mathematical Statistics and an elected member of the International Statistics Institute. *Id.*

In his report, Dr. Wells does not offer an opinion about the causal relationship between cardiovascular endpoints and testosterone therapy. Rather, he offers an opinion about the statistical power of various studies to detect increased risk of major adverse cardiovascular events ("MACE"). Specifically, Dr. Wells opines:

> Most of the extant studies examining between exogenous testosterone therapy and MACE have quite limited power to detect a 50% increased risk. These studies are essentially unable to rule out an increased risk of a MACE due to testosterone therapy and thus fail to prove, or provide assurance about the safety. If one correctly performs a Bayesian inferential meta-analysis methodology using the event count data, there is roughly an 85% probability that testosterone supplementation increases the odds of a MI and stroke. This posterior probability reveals that although a frequentist 95% confidence interval of 0.78 - 2.72 includes the value one, there a high posterior probability of a MACE event with testosterone supplementation.

Ex. 2, Wells Report at 2.

Dr. Wells' report details the basis of this opinion, in particular, explaining the difference between Type I errors (false positives) and Type II errors (false negatives). *Id.* at 2-4. He explains the role of so-called "confidence intervals" and statistical power in helping to control both Type I and Type II errors. *Id.* Applying these concepts, Dr. Wells examined two meta-analyses of testosterone therapy and MACE that failed to find a statistically-significant association. *Id.* at 5-11. He assessed the risk of Type I errors and Type II errors given the size of various studies considered in the meta-analyses. *Id.* He concluded that while the risk of Type I error was controlled, so that the risk of false

positive was low, the studies were not large enough to avoid Type II errors (false negatives) with respect to an increased risk of approximately 50%. *Id.*

Dr. Wells was able to calculate the probability that the two meta-analyses under consideration would fail to detect a true effect of a 50% increased risk – that is, return a false negative – given the sample sizes of the studies. He found that for one of the meta-analyses, "the probability of a Type II error is an intolerable *71.57%*." *Id.* at 7. The probability of failure to detect a 50% increased risk in the other meta-analysis was 45.45% for one set of endpoints and 74.15% for the other. *Id.* Dr. Wells went on to calculate how large the underlying studies would have to be to bring the Type II error rate down to 20% (also referred to as 80% power). He calculated that for one of the meta-analyses, the sample size would have to have been 3.5 times as large as it was in order to reduce to 20% the probability that the study would fail to detect a 50% risk in cardiovascular endpoints. *Id.* at 8. Dr. Wells noted that the authors of other studies had calculated that similar sample sizes were needed to reach similar Type II error rates.

Dr. Wells also performed a Bayesian meta-analysis, *see* Ex. 2, Wells Report at 8-10, and a sensitivity and sub-group analysis, *id.* at 10-11, in order to analyze whether TRT increases the risk of heart attacks and strokes in men. His Bayesian analysis showed an 85% probability that TRT does increase the risk of stroke and MI in men. *Id.* at 2; 10. His sub-group analyses showed that in one meta-analysis, a composite cardiovascular endpoint was "significantly associated with testosterone therapy" for duration of less than one year and that there was greater risk for these endpoints with the transdermal formulations. *Id.* at 11. He similarly found that "[t]he more specific MACE (MI and stroke) is significantly associated with testosterone therapy for transdermal formulations." *Id.* He also concluded that "[i]n each of the subgroup analyses, the Type I error rate has been controlled so the chance of a false positive is small." *Id.*

Dr. Wells offered similar opinions with respect to the both the AbbVie and the Auxilium bellwether cases. AbbVie moved to exclude his opinion; the Court denied the motion. *See* CMO 46. The Auxilium Defendants did not seek to exclude Dr. Wells' testimony.

Hossein Ardehali, M.D., Ph.D.

Dr. Hossein Ardehali is a cardiologist and research physician with both an M.D. and a Ph.D. in molecular physiology and biophysics from Vanderbilt University. He is board- certified in cardiovascular medicine and is a Fellow of the American College of Cardiology and the American Heart Association. Ex. 3, Ardehali General Report at 2. Dr. Ardehali is currently a tenured professor of Medicine – Cardiology and Pharmacology at the School of Medicine, Northwestern University, as well as the Director of the Center for Molecular Cardiology there. *Id.* Dr. Ardehali has previously provided general and specific causation opinions in this MDL; his credentials were discussed in detail in the briefing on the AbbVie Defendants' motions to exclude those opinions.

In this case, Dr. Ardehali has provided six reports: a general causation report ("Ardehali General Report") and supplement ("Ardehali Supplemental General Report") and case-specific reports with respect to the cause of Plaintiffs Martin's and Brubaker's heart attacks and supplements to both (respectively, the "Ardehali Martin Report" and "Ardehali Brubaker Report"). In his general causation report, Dr. Ardehali offers twenty opinions concerning cardiovascular disease and testosterone supplementation. *See* Ex. 3, Ardehali General Report at 105-108. Key among these opinions are Dr. Ardehali's opinions that: (a) "[e]xogenously administered testosterone therapy in men increases the risk of a major cardiovascular event (myocardial infarction or cerebrovascular accident) through rheological, biochemical, and coagulation system effects that can affect the integrity of blood flow within the coronary artery or cerebrovascular circulations," *id.* at 105; (b) [t]he adverse effects of exogenously administered testosterone therapy are amplified in subpopulations of men who have preexisting conditions associated with increasing levels of atherosclerotic burden and an underlying chronic inflammatory state," *id.*; (c) "[t]here is a considerable body of evidence that identifies low endogenous testosterone levels in the setting of non-classical hypogonadism as a biomarker of diminished health and risk for major cardiovascular event in middle-aged and older men; (d) "[t]here was and is a lack of long-term safety [data] regarding the administration of testosterone therapy to middle-aged and older men with decreased levels of testosterone related to aging or comorbid conditions which frequently accompany the aging process," *id.* at 106; (e) "The evidence

demonstrates that the administration of exogenous testosterone to middle-aged and older men who are diagnosed with testosterone declines unrelated to classical hypogonadism is dangerous because it increases the risk of coronary artery and cerebrovascular occlusive events (heart attack and stroke)," *id.* at 106-07; and (f) "[k]nown mechanisms of action existed at the time of Androderm launch which would have informed a reasonable pharmaceutical company that the administration of testosterone to men with significant cardiovascular risk factors was unsafe and potentially created an unreasonable risk." *Id.* at 108.

In his Martin case-specific report, Dr. Ardehali reviews Mr. Martin's medical history, noting he has several common conditions, all well managed. Ex. 4, Ardehali Martin Rpt. at 2-3. He also detailed the events surrounding Mr. Martin's Androderm prescription, particularly noting that Mr. Martin inquired whether his chronic fatigue could be due to low testosterone and requesting his physician trial him on TRT once the values came back as low normal. *Id.* at 5. And, he examined the circumstances of Mr. Martin's myocardial infarction and his treatment for it, particularly noting that, having reviewed the catheterization lab report and the catheterization images, Dr. Ardehali agreed with the findings in the report. *Id.* at 6-7.

Dr. Ardehali analyzed Mr. Martin's ten-year risk of having a cardiovascular event at the time of his MI, using the Framingham Risk Score algorithm and determined that Mr. Martin's ten-year statistical risk for a cardiovascular event at that time was 7.3. Importantly, Dr. Ardehali made this calculation using every factor the Framingham algorithm treats as a potential risk for a cardiovascular event, but not factoring in the role testosterone replacement therapy played.

Dr. Ardehali explains that Mr. Martin's MI was caused in part by the effect testosterone has on increasing atherosclerotic burden and in part by the pro-thrombotic effect caused by the TRT. He concludes: "But for the use of the Androderm testosterone product, Mr. Martin would not have experienced the MI and myocardial damage." Ex. 4, Ardehali Martin Report at 14. He further explains that "[t]he Androderm therapy was a substantial factor in causing this myocardial infarction event because of its effects on coagulation under circumstances of a systemic chronic inflammatory disease." *Id.*

In his Brubaker case-specific report, Dr. Ardehali reviews Mr. Brubaker's medical history, noting he has several pre-existing medical conditions. Ex. 5, Ardehali Brubaker Rpt. at 2-3. He also detailed the events surrounding Mr. Brubaker's Androderm prescription, particularly noting that Mr. Brubaker inquired whether he had "Low T" after seeing commercials and requesting his physician prescribe him TRT. *Id.* at 4. And, he examined the circumstances of Mr. Martin's myocardial infarction and his treatment for it. *Id.* at 4 6.

Dr. Ardehali analyzed Mr. Brubaker's ten-year risk of having a cardiovascular event at the time of his MI, using the Framingham Risk Score algorithm and determined that Mr. Brubaker's ten-year statistical risk for a cardiovascular event at that time was 12.9%. Importantly, Dr. Ardehali made this calculation using every factor the Framingham algorithm treats as a potential risk for a cardiovascular event, but not factoring in the role testosterone replacement therapy played.

Dr. Ardehali explains that Mr. Brubaker's MI was caused in part by the effect testosterone has on increasing atherosclerotic burden and in part by the pro-thrombotic effect caused by the TRT. He concludes: "But for the use of the Androderm testosterone product, Mr. Brubaker would not have experienced the MI and myocardial damage." Ex. 4, Ardehali Brubaker Report at 111. He further explains that "The Androderm therapy was a substantial factor in causing this myocardial infarction event because of its effects on coagulation under circumstances of a systemic chronic inflammatory disease." *Id.*

This Court has previously denied a motion to exclude Dr. Ardehali's general causation opinion in the AbbVie bellwether cases and similarly denied motions to exclude Dr. Ardehali's case-specific opinions in both the AbbVie and Auxilium bellwether cases. *See* CMO 46, CMO 76. (Dr. Ardehali also offered a general causation opinion for the Auxilium bellwether cases; the Auxilium Defendants did not seek to exclude it.)

Robert W. Johnson

Robert W. Johnson is an economic damages expert. He has an educational background in business administration, economics, finance, and investments. *See* Ex. 17, Johnson Original Report at

20-23. He holds a B.A. in Business Administration with a major in economics from Baruch College and has an MBA from Stanford University with a major in finance and investments. *Id.* He has practical experience, skill, and training from his time working as (i) a securities analyst Donaldson, Lufkin & Jenrette where he analyzed and made stock recommendations to the 100 largest financial institutions in the United States; (ii) a securities analyst and portfolio manager for American Express Investment Management Co. where he analyzed and made stock recommendations for six industries and managed part of a $700 million mutual fund; (iii) an Assistant to the Vice President of HRB Singer, Inc. where he directed corporate acquisition policy and special situations analysis of corporate divisions; and (iv) an Assistant to Group Controller for FMC Corp where he coordinated and approved all capital expenditures ($75 million per year) for the $2.5 billion Defense Group. He also has been performing economic and damage analyses for more than 35 years in his time at Legal Economic Evaluations Inc. and Robert W. Johnson & Associates. *Id.* From this background, Mr. Johnson is qualified to examine and calculate a company's financial condition. Mr. Johnson opines that Actavis plc is a "strong and stable company" with a net worth of $73.8 Billion. *See* Ex. 6, Johnson Suppl. Rpt. at 1. His opinions are based upon a valid methodology for his field as he determined Actavis plc's financial condition based upon his review of financial data from Securities and Exchange Commission ("SEC") filings as well as news releases from the company and market capitalization data from Yahoo! Finance. His proposed testimony will assist the jury because this type of financial analysis is beyond the knowledge and skill of a lay juryperson.

The Court previously held that Mr. Johnson's expert testimony was unnecessary in the AbbVie bellwether trials because AbbVie stipulated to its net worth. The Actavis Defendants have not stipulated to any entity's net worth.

LEGAL STANDARDS

This Court has set forth the legal standards to be applied on a motion under Fed. R. Evid. 702 in its ruling on the AbbVie defendants' motion to exclude the testimony of plaintiffs' experts. *See* CMO 46, Dkt. No. 1895 (May 8, 2017); CMO 48, Dkt. No. 1897 (May 8, 2017).

ARGUMENT

The testimony of Drs. Gerstman, Wells, and Ardehali, and Robert Johnson will assist the trier of fact by explaining scientific and technical material concerning testosterone and heart disease.

Actavis asserts that Plaintiffs have no reliable expert testimony regarding general causation – that testosterone is capable of causing heart attack – criticizing the studies and meta-analyses upon which Dr. Gerstman, Dr. Ardehali, and Dr. Wells rely. Plaintiffs respectfully ask the Court to continue to reject these attacks. When these arguments were first raised during the AbbVie bellwether process, this Court stated: "Ultimately, experts on both sides of this litigation have analyzed the existing epidemiological evidence in detail, criticizing the studies on which the other side relies, and drawing different conclusions from the literature. This is not a case in which plaintiffs' experts have simply cherry-picked the favorable studies while ignoring unfavorable studies entirely." CMO 46, *citing In re Zoloft (Sertaline Hydrochloride) Prod. Liab. Litig.*, 26 F.Supp.3d 449, 460-61 (E.D. Pa. 2014); *In re Rezulin Prod. Liab. Litig.*, 369 F.Supp.2d 398, 425-26 (S.D. N.Y. 2005). "At this stage, it is not the Court's role to choose between competing studies. The studies' merits and demerits can be explored at trial. *Id.* (internal citations omitted).

On the case-specific side, Dr. Ardehali's differential etiology in these cases mirrors the requirements of the Seventh Circuit and the demands of *Daubert v. Merrell Dow Pharm., Inc.,* 509 U.S. 579 (1993). As this Court has previously recognized, "a differential diagnosis, also referred to more accurately in this context as a 'differential etiology,' is a reliable methodology for making a specific-causation determination." CMO 46 at 42, *citing Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 433 (7th Cir. 2013) (differential diagnosis and differential etiology are "generally accepted means for evaluating the cause of a plaintiff's injury"). In "a differential etiology, the doctor rules in all the potential causes of a patient's ailment and then by systematically ruling out causes that would not apply to the patient, the physician arrives at what is the likely cause of the ailment." *Id.* As the Seventh Circuit has held, there "is nothing controversial about that methodology." *Id.* A differential etiology "satisfies a *Daubert* analysis if the expert uses reliable methods." *Brown v. Burlington N. Santa Fe Ry. Co.*, 765 F.3d

765, 772 (7th Cir. 2014). This Court has already held that a properly-conducted differential etiology "is a reliable methodology for making a specific-causation determination." *See* CMO 46 at 42.

The standard for proper differential etiology under *Daubert* does not require an expert to rule out every alternative cause. *Schultz*, 721 F.3d at 434. The court "may consider whether they adequately account for obvious alternative explanations." *Id.*, *quoting* Fed. R. Evid. 702 Committee Note (2000) (internal quotations omitted). *See also, e.g., Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 265 (4th Cir. 1999) (a "medical expert's causation conclusion should not be excluded because he or she has failed to rule out every possible alternative cause of a plaintiff's illness."). "[O]nly 'where a defendant points to a plausible alternative cause and the doctor offers no explanation for why he or she has concluded that was not the sole cause'" is that doctor's methodology unreliable. *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 156 (3d Cir. 1999). The expert "must provide a reasonable explanation as to why he or she has concluded that [any alternative cause suggested by the defense] was not the sole cause of the plaintiff's injury." *Guinn v. AstraZeneca Pharms. LP*, 602 F.3d 1245, 1253 (11th Cir. 2010) (internal quotations omitted). As discussed more fully below, Dr. Ardehali's methodology in these cases is identical to that previously admitted in his general and case-specific reports, and should be admitted here once again.

I. DR. GERSTMAN, DR. WELLS, AND DR. ARDEHALI'S OPINIONS RELATED TO GENERAL CAUSATION SHOULD NOT BE EXCLUDED

Actavis does not challenge the qualifications of Plaintiffs' causation experts. Instead, it focuses its attack on the reliability of the methodologies the experts use in reaching their opinions that TRT is capable of causing Plaintiffs' alleged injuries. Actavis asserts that the following are all prohibitively unreliable: (1) composite endpoints; (2) Bayesian meta-analyses; (3) Plaintiffs' proposed mechanisms of injury; (4) the testosterone epidemiological studies; and (5) animal and *in vitro* studies. Actavis also argues that Plaintiffs' experts' opinions are irrelevant because Plaintiffs are too young. All of these arguments fail. Dr. Gerstman, Dr. Wells, and Dr. Ardehali use reliable methodologies in reaching their opinions. Plaintiffs' experts appropriately consider the totality of the evidence in forming their

opinions. *See, e.g., In re Tylenol (Acetaminophen) Mktg., Sales Practices, & Prod. Liab. Litig.,* 198 F.Supp.3d 446, 458 (E.D. Pa. 2016) (where expert based causation opinion on "totality of the evidence," including clinical trials, animal studies, case reports, and his own clinical experience, opinion was reliable and admissible). Dr. Gerstman, Dr. Wells, and Dr. Ardehali consider and address the purported flaws of the studies on which they rely and also offer their own criticisms of the studies that have not found any association between TRT and increased cardiovascular risk. *See* CMO 46 at 25. As this Court has held before, Plaintiffs' experts' totality of the evidence approach is a reliable one because of how they have applied it. They have not, for example, cherry-picked studies or failed to grapple with contrary evidence. Plaintiffs' experts address each study individually, pointing out the merits and demerits of each. Actavis, like AbbVie, is likely correct that no single piece of evidence the experts rely upon is sufficient to support their causation opinions. But the experts have adequately explained why they have reached their conclusions on the basis of the evidence as a whole. *See* CMO 46 at 32, *citing Milward v. Activity Specialty Prod. Grp., Inc.,* 639 F.3d 11, at 23 (1st Cir. 2014). The Court's inquiry at this stage is to determine whether the experts "considered sufficient data to employ the methodology," not whether their consideration of the data led to the correct conclusion. *Stollings v. Ryobi Techs., Inc.*, 725 F.3d 753, 766 (7th Cir. 2013). For an expert conclusion that is subject to doubt, "[i]t is the role of the jury to weigh these sources of doubt." *Id.*

A. Composite Endpoints

Actavis argues that Dr. Gerstman, Dr. Wells, and Dr. Ardehali impermissibly rely on some version of cardiovascular event composite endpoints in support of their opinions related to general causation. Plaintiffs' experts' consideration of composite endpoints does not make their opinions unreliable.

Composite endpoints can be very helpful to statistical analysis, particularly where the existing studies are, as here, underpowered. Actavis' own statistician agreed with the FDA that composite endpoints can provide a substantially higher overall event rate that allows a study with a reasonable sample size and study duration to have adequate power. Ex. 7, Kevin Kip Tr. at 209-210. ("[O]f the factors that influence statistical power, low event rates generally have less power, and so [the FDA] is

suggesting that if you put together multiple endpoints, such as death, MI, and stroke, there are more events, which, assuming the same relative risk, will increase statistical power."), *citing* FDA Draft Guidance, Multiple Endpoints in Clinical Trial, attached as Ex. 8. As Dr. Kip concedes, the FDA exemplifies the benefit of using composite endpoints by pointing to the analysis of myocardial infraction, stroke, and death together. *See* Ex. 7, Kip Tr. at 211; Ex. 8, Draft Guidance at 19. Dr. Kip also agreed that the testosterone therapy studies and trials are all low power because of the small number of event rates and sample size. Ex. 7 at 210-211 ("The individual studies overall were underpowered with respect to cardiovascular events."). Ultimately, Actavis' own expert, Dr. Kip, agreed that it was, not only appropriate, but best practice to use composite endpoints given these facts. *Id.* at 211:6-9.

Dr. Gerstman, Dr. Wells, and Dr. Ardehali testified that reporting individual, component endpoints separately can sometimes be good statistical practice. *See* Ex. 9, Gerstman Tr. at 132; Ex. 10, Wells Tr. at 99; Ex. 11, Ardehali Tr. at 59-60; 193. However, as Dr. Gerstman qualified, it is not required practice. *See* Ex. 9, Gerstman Tr. at 132; 137-8 ("[B]ecause if you analyze every permutation of endpoint, you are endlessly doing analyses and you are running into the problem we discussed previously, that of multiplicity"); *see also id.* at 139 (stating whether to analyze component endpoints "would depend upon the research question and the available data and the limitations therein"); and *Id.* at 144 ("When feasible and when appropriate"). Dr. Ardehali opined that "you have to make sure that the study is powered enough to look at those specific [composite] endpoints." Ex. 11, Ardehali Tr. at 196.

Plaintiffs' experts reliably utilized composite endpoints where limited data was available. *Id.* at 203-204 (Where "limited data [is] available" it is appropriate to "use the data you have and get the best results out of it"). Dr. Gerstman testified that the objective of his report was to address the relation between testosterone therapy and arterial thromboembolism. *See* Ex. 9, Gerstman Tr. at 131. He opined that it was beneficial for him to analyze composite endpoints for the purpose of his meta-analysis given the insufficient number of cases reported in clinical trials. *Id.* ("If you have too few cases, a very small power for individual endpoints, then you're spinning your wheels by comparing,

say, six cases to ten cases."). Due to the small number of events, Dr. Gerstman testified that an analysis of the individual endpoints was not appropriate. *Id.*

Actavis' own statistical expert, Dr. Kip, conceded that even he did not follow every "gold standard" procedure in the analysis of composite and component endpoints. Ex. 7, Kip Tr. 213-215 (admitting that he did not use a multiple correction procedure to address the issue of the potential false finding he could get from multiplicity in looking at both composite endpoints and component endpoints), *citing* FDA Draft Guidance, Ex. 8. Dr. Kip's failure to adhere to these procedures is certainly territory for cross-examination, but not exclusion. The same is true for Plaintiffs' experts' reliance upon composite endpoints without further analysis of the component endpoints.

Plaintiffs' experts have analyzed all existing evidence in detail, criticized the evidence on which Actavis relies, and have drawn conclusions from the evidence that differs from that of Actavis' experts. This is not a case in which Dr. Gerstman, Dr. Wells, and Dr. Ardehali have simply cherry-picked the favorable studies while ignoring unfavorable studies entirely. "At this stage, it is not the Court's role to choose between competing studies." CMO 46 at 28, *citing Schultz,* 721 F.3d at 433. The studies' merits a demerits can be explored at trial. *Id.*

B. Bayesian Meta-Analyses

Actavis argues that Dr. Gerstman and Dr. Wells improperly rely upon Bayesian meta-analyses. Bayesian analysis is a reliable, well-accepted methodology that has been the subject of extensive peer-reviewed analysis. Meta-analysis is a method of pooling study results to arrive at a single figure to represent the totality of the studies reviewed. *See* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (3d ed. 2011) ("RMSE" or "Reference Manual") at 607; *see also id.* at 581 n.89. By combining the data from multiple studies, meta-analyses can add to the understanding of data that has been derived from small, underpowered studies (as is the case in most of the clinical trials of testosterone). As the Reference Manual explains, "In a meta-analysis, studies are given different weights in proportion to the sizes of their study populations and other characteristics." RMSE at 607. Courts have recognized that meta-analysis is a regularly used and (when properly performed) reliable scientific technique. *See In re Paoli Railroad Yard PCB Litigation, 916 F.2d 829, 856–57 (3d Cir. 1990); In*

re Bextra and Celebrex Marketing Sales Practices and Product Liability Litigation, 524 F.Supp.2d 1166, 1184 (N.D. Cal. 2007); and CMO 46.[3]

Actavis' expert, Dr. Kevin Kip, testified there are "competing schools of thought" regarding whether the Bayesian or the "frequentist" approach is a better statistical method. *See* Ex. 7, Kip Tr. at 52-53 ("[W]hen I studied at the University of Pittsburgh they taught all frequentist statistics and across the street at Carnegie Mellon they taught Bayesian statistics"). However, as Dr. Kip states, it is merely "personal preference." *Id.* at 53. In fact, the FDA has issued guidance that authorizes for purposes of industry the ability to use either frequentist or Bayesian methods in designing and analyzing clinical trials. *Id.* at 54-55. While Bayesian methods have not been frequently utilized in the context of pharmaceutical drugs and medical devices in the past, they are becoming more common. *See* Ex. 10, Wells Tr. at 194. "Now, people use Bayesian methods for very complex models." *Id.* at 200. Moreover, this Court has held that these specific meta-analyses are reliable. *See* CMO 46 at 29-31. As AbbVie conceded, Bayesians are "a well-established minority" in the field of statistics. *Id.* at 29, *citing* RSME at 529.

Because meta-analyses combine the results from multiple studies, the number and quality of the underlying studies, their compatibility for meaningful combination, and the method used to combine their results are all important factors in assessing the soundness of any particular meta-analysis. Plaintiffs' experts' analysis of the meta-analyses was painstaking, with detailed explanations of the strength and weakness of each one. After careful review, they concluded that the scientific research showed that Androderm caused an increased risk of cardiovascular events.

There are many different ways to analyze data and perform meta-analyses using Bayesian approaches. *See* Ex. 10, Wells Tr. at 187. Actavis argues that Plaintiffs' experts' specific approach to their Bayesian meta-analyses, based on John Carlin's "Meta-Analysis for 2x2 Tables: A Bayesian

[3] For additional background, Plaintiffs thoroughly discussed Bayesian analysis during the AbbVie bellwether process. *See* Pls.' Br., Dkt. No. 1812. Plaintiffs incorporate those arguments herein.

Approach," is unreliable because of limited data sets. Carlin's approach, Actavis argues, only works with very large sample size data sets form which to draw. Actavis is wrong.

Actavis' expert, Dr. Mark Weisberg, admitted that there were "adequate number of trials that were included by Dr. Gerstman and Dr. Wells in their Bayesian analysis" but "not enough data within each one of trials." Ex. 12, Weisberg Tr. at 183. Yet Dr. Wells testified numerous times during his deposition that Carlin's small data set concern is not nearly as important as the distribution of the log odds ratio when plotting the data. *See* Ex. 10, Wells Tr. at 190 ("[I]t really depends on the distribution of the plot estimates"); *Id.* ("[T]he model is about the distribution of the log odds ratio, because that's what's normal, not the – not related to the counts, it's just related to what the log odds ratio is"); *Id.* at 192 ("Yes, the [observed counts are] small, but the model implicit here is about the distribution of the log odds ratio; it's normal with something. So I think that's – it's probably true, because, you know, whenever you have small counts, you get more variability, but the model itself is all about the distribution of the log odds ratio"); *Id.* at 201 ("And again, it's the distribution of the odds ratio – the log odds ratio – not necessarily the event counts").

Dr. Wells testified that he plotted the estimates onto a histogram and the log odds ratio distribution appeared appropriately distributed. *Id.* at 190. In short, Plaintiffs' experts have adequately explained why their particular utilization of their meta-analyses are reliable. But perhaps more importantly, Actavis points to no legal authority to support their argument that the meta-analyses here should be excluded. Actavis' further argument regarding study biases and lack of peer review and publication are appropriate areas for cross-examination but not exclusion.[4] *See* CMO 46 at 30 ("[T]hat is an issue affecting the weight to be accorded to the analysis, not its admissibility").

As described below Plaintiffs' experts did not stop with consideration only of the RCTs, observational studies, and meta-analyses specific to testosterone therapy and cardiovascular disease. They also considered evidence of the mechanism by which testosterone might increase the risks of heart attacks. Thus, they considered biochemical and biomedical research concerning the effects of

[4] This Court held that not publishing a journal article on Bayesian analysis does not render the expert unqualified or the opinions unreliable. *See* CMO 46 at 30.

sex hormones on inflammation, on platelet formation, on reactive oxygen species, and on red blood cell mass and blood viscosity. Noting that estradiol (estrogen) is a metabolite of testosterone (meaning that testosterone may be converted to estradiol in the body), Plaintiffs' experts also considered studies concerning the effects of exogenously administered estrogen on both men and women with regard to cardiovascular events.[5]

Accordingly, as this Court has previously found, Dr. Wells and Dr. Gerstman reliably utilized Bayesian meta-analyses and their opinions should not be excluded.

C. Proposed Mechanisms of Injury

Plaintiffs' experts posit a number of potential mechanisms by which Androderm and other TRT drugs might increase the risk of cardiovascular injuries. Specifically, Plaintiffs' experts suggest TRT is pro-thrombotic – that is, it increases the risk of blood clots – because of its tendencies to increase (1) estradiol, a metabolite of testosterone and a form of estrogen, which has been connected to increased risk of clot formation; (2) thromboxane A2 receptors, which can promote abnormal platelet function and increased risk of clotting; (3) hematocrit (the ratio of the volume of red blood cells to the total volume of blood), which can increase blood viscosity, leading to a higher incidence of clotting; and (4) oxidative stress, which leads to an acceleration of coronary artery plaque volume.

Plaintiffs' experts discuss the plausibility of the biological mechanism in particularly extensive detail, relying on various studies and their biological knowledge to explain how elevated estradiol, thromboxane, hematocrit, and oxidative stress, among other mechanisms, may increase cardiovascular risk. Actavis, like AbbVie, criticizes Plaintiffs' experts mechanism theories because they do not rely on any studies that demonstrate a link between use of TRT in human beings and the proposed mechanism plus a link between the proposed mechanism to cardiovascular events. But Actavis, like AbbVie, cites to no authority that says experts must be held to so high a standard in demonstrating the plausibility of mechanism. Rather, an analysis of biological plausibility "asks whether the

[5] Although Plaintiffs' experts consider the mechanisms by which testosterone may increase the risks of cardiovascular events, they do so primarily to understand biological plausibility and to understand the likely reasons behind the data showing this increased risk (as well as, elsewhere, to establish that, knowing of these mechanisms, Actavis knew or should have known about the dangers of Androderm).

hypothesized causal link is credible in light of what is known from science and medicine about the human body and the potentially offending agent. *Milward*, 639 F.3d at 26. It is sufficient for Plaintiffs' experts to provide independent valid bases for determining that the link between TRT and the proposed mechanism is credible and that the proposed mechanism is also credibly linked to the alleged injury. CMO 46 at 29.

1. Estradiol

Plaintiffs' use of analogous evidence does not render their opinions unreliable. Actavis argues that Drs. Gerstman and Ardehali cherry-pick certain portions of estrogen studies and improperly extrapolate from clinical trials in women showing increased estradiol associated with CV events to men on TRT. This might be so if evidence from hormonal contraceptives or hormone replacement therapy were the only evidence on which these experts based their opinions. But, as described throughout this brief, that is clearly not the case. The opinions of Drs. Gerstman and Ardehali are solidly grounded in studies specifically involving TRT therapy in men. That the evidence of these studies is further confirmed by analogous studies – the effect of estradiol (a metabolite of testosterone) on cardiovascular risk in women taking hormonal contraceptives – does not make the experts' opinions less reliable.

Indeed, testosterone manufacturers looked at the analogy between heightened risks of clotting associated with estrogen use in women (as shown in studies involving oral contraceptive pills and so-called estrogen HRT ("hormone replacement therapy")) and the potential of testosterone to increase such risks. *See* Pls.' Br. (Dkt. No. 1812) at 57-58. Testosterone clinical trials measured subjects' estradiol levels specifically because estradiol is a metabolite of testosterone and is associated with CV events in women on hormone replacement therapy. *See* AbbVie Causation Br. (Dkt. No. 1748) at 15. Plaintiffs' experts' consideration of the same evidence that TRT manufacturers looked at (albeit with different conclusions) does not make the opinions unreliable. Regardless, an expert is permitted to extrapolate from the available data. *See C.W. v. Textron, Inc.*, 807 F.3d 827, 833 (7th Cir. 2015) (experts can extrapolate from available data when data is not available that addresses the impact of an agent in the precise population at issue). Plaintiffs' experts properly extrapolated from women to men here.

This Court rejected AbbVie's argument that Plaintiffs' experts' consideration of HRT studies rendered their opinions unreliable (*see* CMO 46 at 33-34) ("[T]he fact that testosterone metabolizes into estradiol makes it reasonable to consider how increased levels of estrogen affected women under hormone therapy. Indeed, such evidence could be particularly relevant for analyzing the plausibility of increased estradiol as a mechanism"). Plaintiffs' respectfully request that the Court continue to do so as it relates to Actavis.

2. Hematocrit

Plaintiffs' experts opine that testosterone therapy affects red cell mass and the rheological properties of blood through the arterial system. *See, e.g.,* Ex. 3, Ardehali Rpt. at 75. Dr. Ardehali states that the "erythropoietic-stimulating effects of androgens have been known for well over half a century." *Id.* Actavis does not make any specific arguments regarding Dr. Gerstman's opinions regarding hematocrit. Instead, Actavis centrally argues that Dr. Ardehali's "principal reliance" for his hematocrit argument is only on one flawed observational study that found a positive association between elevated hematocrit and cardiovascular disease mortality in men. *See* Defs.' Br. at 26. Actavis also argues that Dr. Ardehali unreliably supplements that opinion by pointing to several clinical trials related to erythropoiesis and its association with cardiovascular events and mortality.

Dr. Ardehali in no way *principally* relies on the Erikssen study to support his conclusions regarding hematocrit. Dr. Ardehali's report discusses Brown, et al., which assessed the association between hematocrit and CAD in approximately 9,000 adults from the Second National Health and Nutrition Examination Survey. *See* Ex. 3, Ardehali Rpt. at 75. He noted Wells, et al., an article in 1962 for the proposition that for the past half-century, scientists have observed that an increase in red blood cells increases blood viscosity and increases the risk of thrombosis and occlusion. *Id.* He cited Hall's medical textbook, which demonstrates in a chart the steep rate of rise of blood viscosity with incremental changes in hematocrit. *Id.* at 75-76. He also relied on the Framingham Heart Study that observed higher cardiovascular disease mortality in men who had higher hematocrit values. *Id.* at 76; *see also* Carter, et al., Sorlie, et al., and Kunnas, et al. (supporting association between hematocrit levels and CV events). Moreover, Erikssen's observational study reported positive associations between

elevated hematocrit and CAD mortality in men. *Id.* Erikssen fits within the totality of evidence upon which Plaintiffs' experts may appropriately rely.

Dr. Ardehali supplements his opinion regarding the hematocrit mechanism with studies regarding erythropoiesis, or the endogenous production of erythropoietin. These studies concluded that erythropoietin therapies increase cardiovascular events and mortality. Dr. Ardehali observed that these trials observed statistically significant increases in cardiovascular and all-cause hospitalizations in the higher hemoglobin group. *See* Ex. 11, Ardehali Tr. at 89. He also clarified that MI component endpoints do not show a statistically significant increase in high hemoglobin groups because of the very small number of events involved as compared to the sufficiently powered composite endpoints. *Id.* ("The numbers are very small. There is no difference between the two groups … [G]iven that the numbers are very small for myocardial infarction, there is no difference"); *see supra* at Section I.A. The composite endpoints support the conclusion that erythropoietin is associated with increased cardiovascular events.

Actavis makes a myopic attack on one study while ignoring the other surrounding totality of evidence. Drs. Gerstman and Ardehali appropriately included Erikssen's observational study and various studies regarding erythropoiesis in their consideration of whether testosterone therapy affects red cell mass and the rheological properties of blood through the arterial system. Plaintiffs' experts have credibly relied upon various evidence regarding hematocrit. Accordingly, Dr. Gerstman and Dr. Ardehali's opinions regarding hematocrit should not be excluded.

3. Thromboxane

Actavis argues that Plaintiffs' experts inappropriately rely on Ajayi, a small clinical trial that found an association between testosterone injections in young, healthy men with normal testosterone levels and an increase in platelet aggregation. In essence, just as AbbVie did, Actavis argues that studies about different TRT formulations that are administered to a population that is different from the target population for Androderm are, by themselves, insufficient data on which to base an expert opinion about Androderm. *See* CMO 46 33. But the studies are not so disconnected from the facts of this case that they render Plaintiffs' experts' opinions unreliable. *Id.* In other words, Plaintiffs' experts

have not performed an unreliable extrapolation of facts from young, healthy men to older men. Evidence that disparate levels of testosterone in young, healthy men have adverse effects may shed light on the effects of different testosterone formulations use in older men. *Id.* at 34. An expert is permitted to extrapolate from the available data. *See C.W. v. Textron, Inc.*, 807 F.3d 827, 833 (7th Cir. 2015). Thromboxane's association with cardiovascular events is also supported by several other studies and publications. *See* Ex. 3, Ardehali Rpt. at 119 (relying on Ferenchick, Davi, et al., Hilal-Dandon, et al., Cheng, et al., Pearson, et al., Halushka, et al., and Matsuda, et al.); Ex. 1, Gerstman Rpt. 134-135 (relying on Moncada, Nakao, and Gryglewski, et al.). Actavis again attacks one study and ignores the surrounding evidence. Taken together, Plaintiffs' experts' opinions regarding thromboxane are reliable and will assist the jury.

4. Plaque Volume

Plaintiffs' experts opine that TRT increases coronary artery plaque volume. Actavis contends that Dr. Ardehali and Dr. Gerstman inappropriately rely on Budoff, et al. (the so-called "Cardiovascular T Trial,") a double-blind, placebo-controlled clinical trial using coronary CT angiogram to test the hypothesis that testosterone treatment would slow progression of coronary artery plaque volume and non-calcified plaque as determined by coronary computed tomographic angiography. *See* Ex. 3, Ardehali Rpt. at 88; Ex. 1, Gerstman Rpt. at 90. The groups were balanced with respect to atherosclerosis indicators at baseline because the randomization was effective. *Id.* Compared to the placebo group, testosterone treatment was consistently associated across three measurements with significantly greater increases in non-calcified and total plaque volume. Ex. 3, Ardehali Rpt. at 88; Ex. 1, Gerstman Rpt. at 91. As Dr. Gerstman opined in his report "This is important evidence about the mechanism by which testosterone supplementation increases cardiovascular risk in older men." *Id.* Budoff, et al. demonstrated that treatment with testosterone "causes an increase in plaque size and non-calcified plaque in coronary arteries, which are both factors that increase the risk of heart attack." Ex. 16, Ardehali Suppl. Rpt. at 8. Dr. Ardehali also notes that a recent study by Mohler et al., which repeated all of the analyses of the effect of testosterone in the men who participated in the Budoff study, "in conjunction with Budoff, et al. 2017, further informs

my opinion about TRT and the increase in cardiovascular risk." *Id.* at 11. Plaintiffs' experts reasonably rely on the Cardiovascular T Trial in positing that increases in plaque volume is associated with CV events. Actavis fails to point to any legal authority supporting the exclusion of Plaintiffs' experts' reliance upon the Cardiovascular T Trial in support of their opinions.

5. Animal and In Vitro *Studies*

Actavis claims that Plaintiffs' experts improperly extrapolate from and rely upon animal and *in vitro* studies (studies involving human tissues, blood, etc. carried out in a laboratory) in support of their opinions regarding the various mechanisms of injury at issue here. When appropriately used, especially in conjunction with human epidemiology, opinions based in part on animal and/or *in vitro* studies meet all the requirements of *Daubert* and are admissible. *See, e.g., In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 781 (3d Cir. 1994) (district court abused its discretion in excluding evidence of animal studies); *In re Actos (Pioglitazone) Prod. Liab. Litig.*, No. 12-CV-00064, 2013 WL 6796461, at *12 (W.D. La. Dec. 19, 2013). Even if an effect in animals is of limited relevance in showing the same effect in humans, animal studies are highly relevant to the factor of biological plausibility, which has to do with how living systems may plausibly react. This is precisely what the court held in the *Actos* litigation where, as here, animal studies were offered to show biological plausibility, rather than to establish causation. 2013 WL 6796461, at *12. This is all the more true with *in vitro* studies, which may involve human blood and tissue.

Moreover, this Court previously held that Plaintiffs' experts' reliance on these studies was appropriate because they were "part of a much broader set of evidence and primarily for the purpose of determining biological plausibility, for which animal studies and *in vitro* studies may be among the most useful available evidence." *See* CMO 46 at 34, *citing In re Actos (Pioglitazone) Prod. Liab. Litig.*, No. 12-CV-00064, 2013 WL 6796461, at *12 (W.D. La. Dec. 19, 2013); *Smith v. I-Flow Corp.,* NO-09-l-3908, 2011 WL 12556366, at *3 (N.D. Ill. May 3, 2011). Moreover, experts are permitted to extrapolate from available data. *See C.W. v. Textron, Inc.*, 807 F.3d 827, 833 (7th Cir. 2015). Accordingly, just as was the case for the AbbVie bellwether case, Plaintiffs' experts here reliably relied on animal and *in vitro* studies.

D. Epidemiological Studies: Vigen and Finkle

Actavis complains that Plaintiffs' experts have cherry-picked certain observational epidemiologic studies, such as Vigen and Finkle, to support their opinions. Actavis also argues that those two studies are wholly unreliable. Dr. Gerstman and Dr. Ardehali both reviewed and assessed the scientific literature concerning testosterone and cardiovascular disease. Both considered, in light of all the evidence, whether a causal connection between testosterone and cardiovascular events had been demonstrated to a reasonable degree of medical certainty. This methodology is well-established and well-accepted, all the more so because the scientific literature these experts reviewed and relied on also uses standard, reliable scientific methodologies, whether randomized clinical trials, observational studies, or meta-analyses. *See, e.g., Smith v. I-Flow*, 2011 WL 12556366, *2 (opinion reached after review of "dozens of articles and studies that were "either published in peer reviewed journals, presented at national or international conferences, or contained in leading textbooks" reliable and admissible); *Yasmin & YAZ*, 2011 WL 6302573, at *12 (denying motion to exclude testimony of Dr. Gerstman that was based on his examination and analysis of design of multiple studies); *In re Seroquel Prod. Liab. Litig.*, No. 6:06-MD-1769-ORL-22D, 2009 WL 3806435, at *5 (M.D. Fla. June 23, 2009) (opinion formed by analysis and weighting of published scientific literature reliable and admissible); *In re Vioxx Prods. Liab. Litig.*, 401 F. Supp. 2d 565 (E.D. La. 2005) (where both sides' experts reviewed the same studies and reached different conclusions, both had applied reliable methodologies, and the district court found both sides' expert testimony admissible).

This Court previously held that experts on both sides of this litigation have provided "extensive analysis" of four studies that reported a statistically significant association between TRT and increased cardiovascular events, studies which prompted a petition to the FDA from a public advocacy group and a subsequent investigation of the four studies and the potential risks of TRT. *See* CMO 46 at 6. Two of the four studies that this Court held have been extensively analyzed are the two studies that Actavis complains about here – Rebecca Vigen, et al., *Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels*, 310 JAMA 1829 (2013) (the Vigen study); William D. Finkle, et al., *Increased Risk of Non-Fatal Myocardial Infarction Following*

Testosterone Therapy Prescription in Men, 9 PLOS ONE e85805 (2014) (the Finkle study). This Court rejected AbbVie's arguments that Vigen and Finkle were flawed and unreliable. The Court should reject the same argument made by Actavis now.

Plaintiffs' experts reviewed 17 published observational studies, shown in a chart by Dr. Gerstman's report. *See* Ex. 1, Gerstman Rpt. at 50-52. Among these, the Finkle study, published in 2014, showed more than doubling of the risk of heart attack in testosterone users over the age of 65 (ratio of 2.2:1), and a near tripling of the risk in men under 65 with preexisting heart disease (ratio of 2.9:1). The Vigen study, published in 2013, also showed increased risk of smaller magnitude (composite ratio 1.3:1). *Id.* Actavis alleges that Plaintiffs' experts have ignored Li, et al. Actavis is wrong. Dr. Ardehali analyzed Li, et al. in his Supplemental Report dated March 22, 2018 and found several weaknesses in the study. *See* Ex. 16, Ardehali Suppl. Rpt. at 9-10. Dr. Ardehali noted that the study was underpowered to look at CV events, used narrow CV definitions that excluded large groups of MI patients, and was biased since it was designed and conducted by Eli Lilly employees. *Id.* at 10. For these reasons, Dr. Ardehali's opinions concerning the causal connection between TRT and CV events remain unchanged. *Id.* at 12. Plaintiffs' experts have carefully considered all evidence and applied reliable methodologies.

Like AbbVie, in arguing that Plaintiffs' experts lack a sufficient basis for their conclusions, Actavis emphasizes that the FDA reviewed the same data, specifically the same epidemiological studies, as Plaintiffs' experts but reached a different conclusion about whether TRT is associated with cardiovascular injuries. Actavis, however, has not cited any authority for the proposition that conclusions the FDA makes in its review of available data are legally or scientifically dispositive on the issue of causation. In this context, the FDA's opinions are analogous to the opinion of any other expert in this case. Thus, although the FDA may have a different interpretation of the studies relied upon by Plaintiffs' experts, "it is left to the trier of fact, not the reviewing court, to decide how to weigh the competing expert testimony." *Wipf v. Kowalski*, 519 F.3d 380, 385 (7th Cir. 2008). Plaintiffs respectfully submit that this Court should continue to reject the TRT Defendants' arguments that the

Vigen and Finkle studies are unreliable. Plaintiffs' experts have provided reliable, scientific bases for their opinions such that their testimony should be allowed and Actavis' motion should be denied.

E. **Plaintiffs' Age**

Lastly, Actavis argues that all of Plaintiffs' experts' general causation opinions are unreliable because Mr. Brubaker was 41 and Mr. Martin was 52 when they suffered their heart attacks. This is so, Actavis contends, because all of Plaintiffs' experts' opinions are limited to "older men" and Plaintiffs are not "old" enough. This argument is completely without merit.

Plaintiffs' experts have put forth a wealth of scientific evidence about how testosterone could have caused Plaintiffs' heart attacks, particularly regarding the various biological mechanisms at issue. *See supra* at Section I.C. Moreover, Plaintiffs have relied upon studies that *do* show CV risk associated with TRT use in men under 65 years of age. *See, e.g.,* Ex. 1, Gerstman Rpt. at 51 (showing the Finkle study found almost a tripling of MI risk for men under 65 years with a history of prior heart disease). Plaintiffs' experts' opinions are not constrained to men who have celebrated their 65th birthday. The instant studies and publications are not so disconnected from the facts of these cases that they render Plaintiffs' experts' opinions unreliable. *See* CMO 46 (holding that studies about anabolic steroids and female hormone therapy "may shed some light on the effects" of testosterone in different population pools). Moreover, a certain amount of extrapolation from the available data is perfectly acceptable. *See C.W. v. Textron, Inc.*, 807 F.3d 827, 833 (7th Cir. 2015) (experts can extrapolate from available data when data is not available that addresses the impact of an agent in the precise population at issue).

The jury should hear testimony, backed by accepted medical science, about the possible mechanisms and cause of Plaintiffs' heart attacks and, after cross-examination, decide whether Androderm was a substantial factor in causing those injuries through one or more of the mechanisms described. Accordingly, Actavis' motion regarding Plaintiffs' experts' opinions regarding general causation should be denied.

II. DR. ARDEHALI'S SPECIFIC CAUSATION OPINIONS REGARDING MR. MARTIN AND MR. BRUBAKER ARE ADMISSIBLE

Actavis asks the Court to exclude Dr. Ardehali's specific causation expert opinion in Plaintiffs Martin and Brubaker's cases on the grounds that his testimony is unreliable. This argument should be rejected because Dr. Ardehali's opinions are grounded in a reliable and well-accepted methodology, differential etiology, which he properly performed.

Differential etiology is an accepted method for establishing specific causation. *Myers v. Illinois Cent. R. Co.,* 629 F.3d 639, 644 (7th Cir. 2010). In "a differential etiology, the doctor rules in all the potential causes of a patient's ailment and then by systematically ruling out causes that would not apply to the patient, the physician arrives at what is the likely cause of the ailment." *Id.* As the Seventh Circuit has held, there "is nothing controversial about that methodology." *Id.* A differential etiology "satisfies a *Daubert* analysis if the expert uses reliable methods." *Brown v. Burlington N. Santa Fe Ry. Co.*, 765 F.3d 765, 772 (7th Cir. 2014). This Court has already held that a properly-conducted differential etiology "is a reliable methodology for making a specific-causation determination." *See* CMO 46 at 42.

The standard for proper differential etiology under *Daubert does not* require an expert to rule out every alternative cause. *Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 434 (7th Cir. 2013). The court "may consider whether they adequately account for obvious alternative explanations." *Id.*, *quoting* Fed. R. Evid. 702 Advisory Committee Note (2000) (internal quotations omitted). *See also, e.g., Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 265 (4th Cir. 1999) (a "medical expert's causation conclusion should not be excluded because he or she has failed to rule out every possible alternative cause of a plaintiff's illness."). "[O]nly 'where a defendant points to a plausible alternative cause and the doctor offers no explanation for why he or she has concluded that was not the sole cause'" is that doctor's methodology unreliable. *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 156 (3d Cir. 1999). The expert "must provide a reasonable explanation as to why he or she has concluded that [any alternative cause suggested by the defense] was not the sole cause of the plaintiff's injury." *Guinn v. AstraZeneca Pharms. LP*, 602 F.3d 1245, 1253 (11th Cir. 2010) (internal quotations omitted).

Dr. Hossein Ardehali offers the case-specific opinion in Mr. Martin's case that:

> But for the use of the Androderm testosterone product, Mr. Martin would not have experienced the MI and myocardial damage. The Androderm therapy was a substantial factor in causing this myocardial infarction event because of its effects on coagulation under circumstances of a systemic chronic inflammatory disease.

Ex. 4, Ardehali Martin Rpt. at 14. Likewise, Dr. Ardehali reached a similar conclusion in Mr. Brubaker's case, opining that "Androderm therapy was a substantial factor in causing this myocardial infarction event because of its effects on coagulation under circumstances of a systemic chronic inflammatory disease" and that "[b]ut for the use of the Androderm testosterone product, Mr. Brubaker would not have experienced the MI and myocardial damage." Ex. 5, Ardehali Brubaker Rpt. at 11.

In reaching the conclusions that Androderm was a "substantial factor" in causing Plaintiffs' respective injuries, Dr. Ardehali used a standard differential etiology. First, Dr. Ardehali relied on his own general causation report to "rule in" Androderm as a possible cause of Plaintiffs' heart attacks. Actavis' attack on Dr. Ardehali's differential etiology in this regard relies entirely on the outcome of its separate challenge to Dr. Ardehali's general report. To the extent the Court denies Actavis' motion to exclude his general report – as it should for all the reason set forth *infra* at Section I – Actavis' argument on this point must be similarly rejected.

Secondly, Dr. Ardehali considered the risk profile of each Plaintiff, the presentation of their injury, and the known mechanisms of action of testosterone therapy to determine whether Plaintiffs' preexisting health conditions were alternative *sole* causes of their injuries. In each case, Dr. Ardehali concluded they were not. Rather, these conditions acted in concert with Androderm to cause Plaintiffs' injuries – which would not have otherwise occurred. In arguing that Dr. Ardehali's "ruling out" process was flawed, Actavis simply regurgitates arguments the Court already rejected in CMO 46. Namely, that Dr. Ardehali failed to categorically rule out "all potential causes" of Plaintiffs' cardiovascular injuries. But Dr. Ardehali is *not* required to entirely rule our "all potential causes" of Plaintiffs' injuries. *Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 434 (7th Cir. 2013). Rather, he need only explain why a pertinent risk factor was not the sole cause of the injury. In these cases, he has done precisely that by identifying the relevant mechanism of action based on the presentation of

each respective Plaintiffs' injury and describing the manner in which that mechanism acted upon their established risk profile to cause the injuries at issue.

In the case of Mr. Martin, Dr. Ardehali explained that, prior to Mr. Martin's myocardial infarction in May 2013, his Framingham Coronary Heart Disease 10-Year Risk Year was only 7.3% (meaning that he was considered low risk for coronary heart disease over ten years) before considering the added risk of testosterone therapy. Ex. 4, Ardehali Martin Rpt. at 14. He then explained that the thrombotic episode Mr. Martin experienced in May 2013 was caused by Androderm's tendency to increase atherosclerotic burden in addition to its pro-thrombotic effects thereby amplifying Mr. Martin's underlying (and independently minor) risk factors to cause his myocardial infarction and myocardial damage.

Moreover, it was apparent from Mr. Martin's increased troponin levels and T-wave abnormalities observed on arrival to St. Joseph's hospital that he was suffering from a clot in his coronary vessel. However, Mr. Martin was treated and stabilized with aspirin and heparin which resolved the fresh clot during his transport via life-flight to an out-of-state hospital as demonstrated by the change in his T-wave abnormalities on presentation to Essential Health. Given the presence of a fresh clot in conjunction with Mr. Martin's low risk of coronary heart disease, his minor underlying risk factors, and the addition of testosterone therapy's pro-thrombotic and arthleroslerotic effects, Dr. Ardehali concluded that Androderm caused Mr. Martin's myocardial infarction.

In this way, Dr. Ardehali's proposed testimony is strikingly similar to his own report in the *Mitchell* case, which this Court found to be admissible. The Court described Dr. Ardehali's opinion in the *Mitchell* case:

> Though Dr. Ardehali did not rule these risk factors out as potential causes of Mitchell's heart attack, he does explain in his report why he believes they did not constitute the sole cause of the particular myocardial infarction Mitchell suffered. Dr. Ardehali acknowledges that risk factors other than AndroGel were integral in the formation of the lesions that were found on Mitchell's artery. But Dr. Ardehali explains why, under his theory of the mechanism by which TRT causes cardiovascular injuries, AndroGel played a significant role in causing the "acute thrombotic event" that led to Mitchell's ultimate injury. According to Dr. Ardehali, it is the pro-thrombotic effects of TRT that

> can provoke such events in patients like Mitchell who have already developed atherosclerosis as a result of longstanding risk factors.

CMO 46 at 49. As was true with AndroGel and Mr. Mitchell, Dr. Ardehali's report concerning Mr. Martin explains why and how Androderm played a significant role in causing his heart attack. Rather than ignoring Mr. Martin's other risk factors, Dr. Ardehali explained how they worked together with the pro-thrombotic effects of testosterone and its tendency to increase arthleroscerotic burden to cause his injury.

Likewise, in Mr. Brubaker's case, Dr. Ardehali found that Mr. Brubaker's Framingham 10-year risk score was a moderately-low 12.9% without the added risk of testosterone therapy. Yet despite being only objectively moderate risk even with his pre-existing risk factors, when Mr. Brubaker's physicians attempted to perform a cardiac catheterization during his hospitalization for his myocardial infarction, they discovered that his coronary artery had become so occluded that they were unable to even guide run-through wires across the mid-LAD. Dr. Ardehali concluded this was because Mr. Brubaker's Androderm usage had increased the pre-existing arthlerosclerotic burden on his arteries thereby creating the complete occlusion of his vessel.

Importantly, the Framingham risk calculator provides an objective and dynamic evaluation based on the presence and significance of particular risk factors. That is, the Framingham risk calculator not only considers the presence of conditions like hyperlipidemia or hypertension in determining an individual's future risk, it also considers the severity of the condition and whether is treated or untreated by medication when evaluating its relative contribution to future risk. Thus, considering such a risk evaluation assisted Dr. Ardehali in ruling-out for all relevant non-testosterone therapy related risk factors in his differential etiology in determining whether Androderm was a substantial contributing factor in Plaintiffs' MIs.

Nevertheless, Actavis attacks these evidence-based conclusions, in part, because the hospitals did not perform additional medically unnecessary testing that could have further informed Dr. Ardehali's opinions. Seen for what it is, Actavis' attack on Dr. Ardehali's differential etiologies on this point is not actually an attack on his methodology at all – rather it is an attack on the admissibility of

a differential etiology that is not based on the present or absence of a signature causal biomarker. This is apparent by Actavis' underlying argument that Dr. Ardehali cannot reach a causation opinion without having a specific test result to point to in order to conclusively verify his opinion. But this position is clearly contrary to the accepted differential etiology process. That is, if the existence of absence of a particular biomarker were legally necessary to verify or exclude the presence of a specific mechanism then there would be no utility in the differential process in the first place. For this reason, Dr. Ardehali's opinions regarding the mechanisms of action of testosterone therapy have been previously admitted given that they are well-founded based on clinical studies and peer reviewed medical literature. To argue that he is prohibited from considering these mechanisms in the absence of such signature test results is illogical.

Actavis' final attack on Dr. Ardehali's opinions pertains only to Mr. Brubaker. It argues that Mr. Brubaker was not taking Androderm at the time of his MI so there is no basis for Dr. Ardehali to find a causal relationship. This criticism can be easily dispensed with given that it inappropriately relies, *first*, on Defendant's own misunderstanding of Mr. Brubaker's testimony regarding when he began and ceased using Androderm and, *second*, on its attempt to turn a straightforward factual dispute into a *Daubert* challenge. To be clear, Mr. Brubaker was using Androderm at the time of his injury. In February of 2013, Mr. Brubaker went to his family care medical clinic and asked to be prescribed testosterone replacement therapy. Ex. 13, Brubaker Tr. at 103:3-25. He had seen disease state awareness commercials about "Low T" which referenced getting older and symptoms like fatigue and low sex drive. *Id.* On December 13, 2013, he filled a prescription for Androderm containing sixty (60) patches. Ex. 14, SuperRx Pharmacy Records, 5BRUBAKER00011. He used the Androderm patches from December 2013 through March 2014. *See* Ex. 15, Brubaker Plaintiff's Fact Sheet, Amended July 28, 2017 at 15. He refilled his prescription on February 13, 2014. Ex. 14, SuperRx Pharmacy Records, 5BRUBAKER00012. However, before he finished his prescription, he suffered a massive heart attack in early March 2014, formally diagnosed on March 4, 2014. *See* Ex. 14, Records from Loma Linda University Medical Center, 4BRUBAKER00026. When he arrived at the hospital,

Mr. Brubaker reported using Androderm; also, while he did not do so, he was in fact told to continue using Androderm upon discharge. *See id.* at 4BRUBAKER00097 and 4BRUBAKER00402.

In other words, numerous *contemporaneous* documents demonstrate that Plaintiff was, in fact, taking Androderm at the time of his injury irrespective of whether he had started the second refill of his prescription. Therefore, given multiple sources of evidence demonstrating contemporaneous usage, Actavis raises nothing more than a factual dispute here which simply cannot form the basis for exclusion under *Daubert*. *Smith v. Ford Motor Co.*, 215 F.3d 713, 718 (7th Cir. 2000) ("The soundness of the factual underpinnings of the expert's analysis and the correctness of the expert's conclusions based on that analysis are factual matters to be determined by the trier of fact, or, where appropriate, on summary judgment."); *see also In re Ready-Mixed Concrete Antitrust Litig.*, 261 F.R.D. 154, 166 (S.D. Ind. 2009) ("It is obvious that the nature of the parties' dispute in this regard is essentially factual, and therefore not susceptible to a *Daubert* analysis.") (citing *Deputy v. Lehman Bros.*, 345 F.3d 494, 506 (7th Cir. 2003)).

In short, Dr. Ardehali used the same reliable methodology to develop his opinions that the Court has already accepted and it should do so here once more.

III. THE OPINIONS OF ROBERT JOHNSON SHOULD NOT BE EXCLUDED

Mr. Johnson has the necessary qualifications in the field of economics and finance to render an expert opinion on the financial condition of Actavis plc and, in fact, Actavis does not challenge his qualifications. His opinions are based upon a valid methodology for his field as he determined Actavis plc's financial condition based upon his review of financial data from Securities and Exchange Commission ("SEC") filings as well as news releases from the company and market capitalization data from Yahoo! Finance. His proposed testimony will assist the jury because this type of financial analysis is beyond the knowledge and skill of a lay juryperson. As Mr. Johnson's testimony is reliable, relevant, and not unfairly prejudicial, there is no basis for exclusion. Moreover, because Actavis plc failed to appear for the properly noticed deposition pursuant to Rule 30(b)(6), Plaintiffs are simultaneously contemporaneously filing a motion for sanctions against the Actavis Defendants for failing to attend

a properly noticed Rule 30(b)(6) deposition and for failing to produce requested documents. Plaintiffs are requesting that the Court deny Actavis' motion to exclude the expert testimony of Robert Johnson. For that independent reason, Actavis' motion to exclude his testimony should be denied. Even if the Court were not to grant that, however, Actavis Defendants' Motion to Exclude Mr. Johnson's testimony should be denied.

A. Mr. Johnson's Methodology is Reliable and Proper

Mr. Johnson uses reliable methodology to determine the financial condition of Actavis plc. He examines reliable data to arrive at a reasoned conclusion. Defendants' criticisms of Mr. Johnson's methodology go to the weight of his testimony, not the admissibility.

Rule 702 requires that expert testimony be based on "sufficient facts or data" and is "the product of reliable principles and methods." FED. R. EVID. 702. "Reliability" is a question of the validity of the expert's methodology. *Manpower, Inc. v. Ins. Co. of Penn.*, 732 F.3d 796, 806 (7th Cir. 2013). Judges have "considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). "Rule 702's reliability elements require the district judge to determine only that the expert is providing testimony that is based on a correct application of a reliable methodology and that the expert considered sufficient data to employ the methodology." *Stollings v. Ryobi Technologies, Inc.*, 725 F.3d 753, 766 (7th Cir. 2013). "The reliability of data and assumptions used in applying a methodology is tested by the adversarial process and determined by the jury…" *Manpower, Inc.*, 732 F.3d at 808. "The critical inquiry is whether there is a connection between the data employed and the opinion offered…" *Id.* at 806.

In the present case, Mr. Johnson used a reliable methodology in performing his analysis and reaching his opinions. Mr. Johnson's opinion is that Actavis plc is a "strong and stable company." *See* Ex. 6 at 1. Based on his calculation of Actavis plc's financial condition, he has concluded that it has the ability to pay a significant punitive damage award. *See* Ex. 18, Johnson Tr. at 117-118.

Mr. Johnson reached these opinions by using his education and experience to review and synthesize AbbVie SEC filings, news releases, and market capitalization data from Yahoo! Finance to

calculate and determine AbbVie's net revenues, net revenues per day, net earnings, net worth, cash on hand, cash flows, capital expenditures, free cash, dividends, stock repurchases, research and development expenditures, advertising expenditures, available line of credit, stock market value, and the compensation package for its Chairman and CEO. *See* Ex. 6, generally; Ex. 18, Johnson Tr. at 57-58. These measures reveal Actavis plc's financial condition from an economic health, economic wealth and economic status perspective. *See* Ex. 6. It is clear that Mr. Johnson reviewed ample financial data to reach his conclusion and his analysis is within the competence of someone with his background in economics and finance. There is a rational connection between the data he reviewed and the opinion he reached, and, therefore, his methodology is reliable. *See Manpower, Inc.,* 732 F.3d at 809; *Tuf Racing Prods., Inc. v. Am. Suzuki Motor Corp.,* 223 F.3d 585, at 591 (7th Cir 2000).

The fact that Mr. Johnson derived his figures from multiple sources does not render his methodology unreliable. This is nothing more than a criticism of the data set Mr. Johnson chose to use, and "[w]hether [an expert] selected the best data set to use . . . is a question for the jury, not the judge." *Manpower, Inc.*, 732 F.3d at 809. "Assuming a rational connection between the data and the opinion . . . an expert's reliance on faulty information is a matter to be explored on cross-examination; it does not go to admissibility." *Id.* Mr. Johnson testified that his valuation methodologies are based upon his

> [T]raining; experience; knowledge of what I learned in valuations at Stanford; mergers and acquisitions at the AMA; and what I've practiced in mergers and acquisitions on Wall Street and in my corporate life.

Ex. 18, Johnson Tr. at 55.

Actavis alleges that Mr. Johnson's methodologies have been deemed unreliable before in *Pooshs v. Phillip Morris USA, Inc.*, 287 F.R.D. 543 (N.D. Cal. Dec. 5, 2012) and *Soto v. BorgWarner Morse TEC Inc.,* 239 Cal. App. 4th 165 (2015). In *Soto*, Mr. Johnson offered evidence about a company's revenues but did not offer evidence about the company's liabilities or expenses. *Soto* at 195. The issue was that revenue information alone does not "tell you anything about" profits, losses, debts, or available credit. *Id.* In the instant case, however, Mr. Johnson performed precisely the analysis sought by the court in

Soto. *See* Ex. 18, Johnson Tr. at 73; 85 (losses); 76, 103-4 (available credit). *Soto* therefore supports admission of Mr. Johnson's opinion regarding Actavis plc here. As to *Pooshs*, first, this is one case interpreting one state's law and making a determination in light of the facts before it. Mr. Johnson has been designated for cases outside of California. Second, Plaintiffs respectfully contend that the court reached the wrong result in *Pooshs*. The court took issue with Mr. Johnson's consideration of the company's "'financial condition' (based on a wide variety of financial statistics)" because California's default rule is to measure only the defendant's net worth (*Pooshs* at 549-550, *citing Neal v. Farmers Ins. Exchange*, 582 P.2d 980 (1978)) and Mr. Johnson's calculations instead included historical data and California only measures defendants' wealth at the time of trial. *Id.* at 550. However, by the court's own admission, California law allows for consideration of financial factors beyond net worth in determining a punitive damages award. As Mr. Johnson has explained in this case, "net worth" can be an extremely misleading figure because a company can have a negative net worth and still be able to pay a punitive damages award. *See* Ex. 18, Johnson Tr. at 18-19. Plaintiffs contend that the Court should have allowed Mr. Johnson to testify as to the financial condition of the defendant in *Pooshs*, and, had it done so, it would have been proper to allow him to consider financial statistics beyond net worth.

Actavis argues that Mr. Johnson inappropriately rounded off numbers in his calculations. However, Mr. Johnson rounded off numbers to one decimal place and explained that he does so "[t]o make it easier to understand." *See* Ex. 18, Johnson Tr. at 52-54; Fed. R. Evid. 702 ("help the trier of fact to understand the evidence"); *See In re Yasmin and YAZ (Drospirenone) Marketing, Sales Practices and Prods. Liab. Litig.*, 2011 WL 6732819 at * 7, No. 3:09-md-02100 (S.D. Ill., Dec. 16, 2011) (Herndon, J.) (holding an economic expert may be particularly helpful to a jury in looking at financial information pertinent to a punitive damages assessment). The figures that Mr. Johnson rounded off are, for example, that Actavis PLC's net worth in 2017 was $71.2 Billion and $76.2 Billion in 2016. *See* Ex. 6, Johnson Suppl. Rpt. at 7. Rounding these decimals allows the jury to more easily digest the numbers at issue, which Rule 702 specifically calls for – expert testimony that will help the trier of fact to

understand the evidence. Actavis has failed to identify any legal authority that provides that rounding numbers to one decimal is an unreliable methodology.

B. Mr. Johnson's Testimony is Relevant and Will Assist the Trier of Fact

Pursuant to Rule 702, expert testimony is relevant if it will "help the trier of fact to understand the evidence or to determine a fact in issue . . ." Fed. R. Evid. 702. Expert testimony is relevant if it will assist the trier of fact with its resolution of any of the issues in this case. *Smith*, 215 F.3d at 718. "The expert need not have an opinion on the ultimate question to be resolved by the trier of fact in order to satisfy this requirement." *Id.* An economic expert may be particularly helpful to a jury in looking at financial information pertinent to a punitive damages assessment. *See In re Yasmin and YAZ (Drospirenone) Marketing, Sales Practices and Prods. Liab. Litig.*, 2011 WL 6732819 at * 7, No. 3:09-md-02100 (S.D. Ill., Dec. 16, 2011) (Herndon, J.).

Actavis argues that Mr. Johnson's testimony is irrelevant because Actavis plc is not a named defendant in either of Plaintiffs' cases. Actavis plc is the publicly-traded parent company (whether directly or indirectly) to all the Actavis entities within this litigation. According to its filings, no entity other than Actavis plc own a substantial share of the various Actavis Defendants. Therefore, Actavis plc is the sole beneficiary of the profits derived from the sale of Androderm. Presumably, the company insures its sub-entities as well. Moreover, Actavis plc was once a defendant with the MDL and the parties consented to its dismissal without prejudice only after entering Case Management Order 22A, which included a stipulated agreement that the remaining Actavis Defendants "agree they will not claim that either Actavis plc or Watson Laboratories Inc., a Nevada corporation, is an indispensable party to any product liability claims filed in these proceedings as such claims pertain to Androderm."

Mr. Johnson's proposed expert testimony is relevant because it will assist the jury in understanding and synthesizing financial evidence drawn from voluminous documents and determining issues pertinent to punitive damages. The ability to identify, summarize, and interpret the significance of pertinent financial information for a large corporation such as Actavis plc, even if publicly available, is beyond the skill-set of a typical juror. As the Court explained in rejecting a Motion to Exclude Mr. Johnson in *In re Yasmin and YAZ* on similar grounds:

> Clearly, it is generally more helpful to the trier of fact and efficient for the Court to present voluminous information in the form of a summary. However, the jury requires someone in possession of the necessary knowledge and expertise to explain the relevant summaries and charts.
>
> Although concededly comprehensible, the Court finds Johnson's report assists the trier of fact in its analysis of issues relevant to the dispute. . .[T]o allow the jury to assess Bayer's wealth with any level of accuracy, an expert is required to determine Bayer's total wealth and explain his findings in a manner helpful to the trier of fact.

Id.

Mr. Johnson's opinion is that Actavis plc is a strong and stable company from an economic health and economic wealth perspective that is able to meet its obligations and, based on its financial condition, it has the ability to pay a punitive damage award. *See* Ex. 6, Johnson Suppl. Rpt. at 1. Mr. Johnson's testimony will help the jury understand the financial evidence before it, rendering his testimony relevant. *See In re Yasmin and YAZ (Drospirenone) Marketing, Sales Practices and Prods. Liab. Litig.*, 2011 WL 6732819 at * 7.

C. Mr. Johnson's Opinions Should Not be Excluded Under Rule 403

There is no basis for excluding Mr. Johnson's testimony pursuant to Rule 403 of the Federal Rules of Evidence. Rule 403 provides that the Court may exclude relevant evidence if "its probative value is substantially outweighed by a danger of one or more of the following: unfair prejudice, confusing the issues, misleading the jury, undue delay, wasting time, or needlessly presenting cumulative evidence." FED. R. EVID 403. Mr. Johnson's testimony is relevant for the reasons set forth above, and it does not implicate substantial concerns of unfair prejudice, jury confusion, or needlessly wasting the Court's time. Actavis argues that testimony regarding its parent company's wealth is only intended to "have the jury base a damage award on an improper, emotional basis." Defs.' Br. at 45. Actavis' sole citation to legal authority is *Common v. City of Chicago*, 661 F.3d 940 (7th Cir. 2011), a criminal case involving the admission of drug evidence at trial. Actavis has failed to identify any relevant legal authority to support its bare allegation that its parent company's economic condition is unfairly prejudicial, confusing, or a waste of the Court's time.

As Justice Breyer explained in his concurrence in *Gore*, "[wealth] provides an open-ended basis for inflating awards when the defendant is wealthy … *That does not make its use unlawful or inappropriate*;

it simply means that this factor cannot make up for the failure of other factors, such as 'reprehensibility,' to constrain significantly an award that purports to punish a defendant's conduct." *BMW of N. Amer., Inc. v. Gore*, 517 U.S. 559, at 591 (1996) (Breyer, J. concurring) (emphasis added); *see also*, *Cortez v. Trans Union*, LLC, 617 F.3d 688, 718 n. 37 (3d Cir. 2010) ("A jury can consider the relative wealth of a defendant in deciding what amount is sufficient to inflict the total punishment."); *White v. Ford Motor Co.*, 500 F.3d 963, 977 (9th Cir. 2007); ("Determining what amount of punitive damages will 'sting' the defendant requires consideration of its *total* wealth, not merely wealth derived from wrongdoing.") (emphasis in original); *Kemp v. Am. Tel. & Tel. Co.*, 393 F.3d 1354, 1365 & n. 9 (11th Cir. 2004) ("wealth and size of the defendant" could be considered in determining size of punitive damage award, even though, under *State Farm*, the wealth of a defendant cannot justify an otherwise unconstitutional punitive damages award). Evidence of Actavis plc's overall and total financial condition does not implicate extra- jurisdictional and unrelated conduct. It is relevant to aid in the calibration of the effect of any punitive damage award and therefore admissible.

CONCLUSION

For the foregoing reasons, Defendants' motion to exclude expert testimony should be denied in its entirety.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on June 8, 2018, I electronically transmitted the foregoing document to the Clerk of the United States District Court using the CM/ECF system for filing and service to all parties/counsel registered to received copies in this case.

/s/ Brendan A. Smith

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